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ANTI-DIABETIC EFFECT OF CANNABIGEROLIC ACID (CBGA) IN STREPTOZOTOCIN-INDUCED DIABETIC RATS

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Abstract:
Aim: To investigate the anti-diabetic effects of cannabigerolic acid in streptozotocin-(STZ) induced diabetic rats.
Materials and methods: The five groups in this study were, Group I -Normal control, Group II-Diabetic control, Group III-Glibenclamide 5 mg/kg p.o., Group IV- cannabigerolic acid 50 mg/kg/p.o. and Group V-cannabigerolic acid 100 mg/kg/ p.o., respectively. The anti-diabetic activity was assessed using blood glucose level and various biochemical parameters like serum total cholesterol level (TC), triglyceride (TG) level, high-density lipoproteins (HDL), total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and Insulin, respectively. The biochemical indicator assessment was done from the each group with 10% w/v homogenate liver for determination of lipid peroxidation-malondialdehyde (MDA), reduce glutathione (GSH) level, superoxide dismutase (SOD) and catalase activity (CAT).
Results: Cannabigerolic acid exhibited an antidiabetic effect by significantly decreased the level of blood glucose, TC, TG, TP and increase HDL as well as serum insulin level. The results of the study demonstrated that the treatment with cannabigerolic acid was significantly ($P<0.05$) and dose-dependently prevented STZ -induced diabetic rats. CBGA were significantly ($p < 0.001$) increased SOD, CAT and GSH level and decrease found in lipid peroxidation ($p>0.05$).

***Conclusions*:** The findings of the study suggest that cannabigerolic acid possess potential antidiabetic activity as it lowers serum glucose level.
Keywords: Diabetes; Cannabigerolic acid; Streptozotocin

Introduction

The ambitious goal of WHO is achieving universal health coverage, but it is one that can and must be achieved to create a healthier and more equitable world. This will need a health-in-all policies approach that also addresses the social, economic and political determinants of health. The significant goals of the Traditional Medicine Program are, to encourage the combination of conventional medication into national social insurance frameworks and to advance the judicious utilization of customary drug through the improvement of specialized rules and global benchmarks in the field of home-grown prescription. In 2005, W.H.O executed a special program for information needs to support clinical trials of traditional medicine in the diagnosis and treatment of diseases[1]. Diabetes mellitus, commonly called as diabetes, Diabetes mellitus metabolic disease in which blood glucose levels increases. Insulin is a hormone that helps moves sugar from the blood into your cells to be stored or used for energy[2]. Type 2 diabetes mellitus (T2DM) is the most widely recognized, representing 90% of patients in these classifications. T2DM is brought about by protection from the activity of insulin joined with an insufficiency in insulin discharge; as of late, useful nourishments and their bioactive mixes are valuable as integral medications for T2DM[3]. The improvement of insulin obstruction in stoutness shows quickened lipolytic movement with expanded arrival of free unsaturated fats (FFA) into the entrance course, which results in a greasy liver malady. These coursing FFA might be cytotoxic by initiating lipid peroxidation and hepatocyte apoptosis. Further, thinks about have indicated that both corpulence and type 2 diabetes debilitate insulin-actuated concealment of glycogenolysis and gluconeogenesis[4]. The association between age and DM has been well documented, and by the year 2020, 12.9% of the world's population will be 60 or older, compared with 9.9% in the year 2000[5]. In many cases, genetics, habits and environment may all contribute to a person's diabetes. To complicate matters, there can be different risk factors for the various forms of the disease. Type I diabetes is generally diagnosed in small children, but advancing age is a risk factor for Type II and gestational diabetes[5]. Specifically, low insulin level trigger entering or leaving ketosis for example the consumption of fat metabolic state. The total impact is result of high blood glucose levels, poor protein fusion, and other metabolic disarrangements, for example, acidosis. Lost blood volume will be supplanted osmotically from water held in body cells and other body compartments, causing lack of hydration and expanded thirst [6,7]. Progressive reductions in β -cell mass contributes significantly to the pathogenesis of Type-2 diabetes. The ability of glucagon-like peptide-1 Receptor agonists, and related peptides such as gastric inhibitory polypeptide to

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enhance β-cell survival and stimulate β-cell growth in pre-clinical studies of diabetic animal models to suggest that these agents could provide a noninvasive means to preserve and restore functional β-cell mass in patients with Type-2 diabetes[8,9]. Some studies shown that there are some medicinal plants extract inhibit the elevation of blood sugar level, this elevation of blood sugar caused due to inhibition of peripheral utilization of glucose which regulated by pituitary hormone, it's also cause glycogenolysis in maturity-onset diabetes[10]. Some number of studies with STZ-induced diabetes mellitus reported that diabetes mellitus can improve the recovery of heart function after ischemia-reperfusion along with decreasing the incidence of arrhythmias[11]. The Diabetes Research Working Group has identified several research areas that present unique opportunities for major advances and changes that will have to be made in the scientific infrastructure to implement this research endeavor. However, prospects for research in diabetes mellitus and research opportunities are much anticipated and progressive on the bases of research evidence. The aim of present study was to investigate the anti-diabetic effects of cannabigerolic acid in streptozotocin-(STZ) induced diabetic rats.

Materials and Methods

Animals

Wistar rats (150–200 g) were group housed (n= 6) under a standard 12 h light/dark cycle and controlled conditions of temperature and humidity (25±2°C, 55–65%). Rats received standard rodent chow and water ad libitum. Rats were acclimatized to laboratory conditions for seven days before carrying out the experiments. All the experiments were carried in a noise-free room between 08.00 to 15.00 h. A separate group (n=6) of rats was used for each set of experiments. The animal studies were approved by the Institutional Animal Ethics Committee (IAEC), constituted for the purpose of control and supervision of experimental animals by Ministry of Environment and Forests, Government of India, New Delhi, India.

Chemicals

Streptozotocin (Sigma-Aldrich) was used in the present study. All other chemicals and other biochemical used in the experiments were of analytical grade from different firms.

Experimental design and treatment protocol

The rats were injected intraperitoneally by a single dose of a prepared solution of STZ (40 mg/kg suspended in 0.1 mol/L citrate buffer at pH 4.5). If the fasting blood glucose (FBG) was more than 300 mg/100 ml after 72 h of STZ injection, the diabetic type 2 models were successful. Approximately 200µl blood was collected from each animal by retro-orbital sinus in 0.5ml Eppendorf tubes containing 20µl of 20% Sodium Fluoride solution. The collected blood was centrifuged at 8000 rpm at temperature18-22ºC for 10 minutes by centrifuge machine. All animals were weighed, randomized and divided into six groups (6 animals each), and were given following treatment for 21 days by oral route[12].

Group I- Normal
Group II- Diabetic rats received only distilled water (negative control)
Group III- Diabetic rats were treated with glibenclamide (5 mg/kg p.o.)
Group IV- Diabetic rats received cannabigerolic acid (15 mg/kg/day p.o.)
Group V- Diabetic rats received cannabigerolic acid (30 mg/kg/day p.o.)

At the end of the 21st day treatment i.e., 24 h after the last dose of the drug and standard drugs the rats were anaesthetized and blood was collected by retro-orbital plexus. After blood withdrawal animal was sacrificed. The serum was separated by centrifugation at 3000 rpm at 4°C for 20 minutes for the analysis of various biochemical parameters.

Biochemical Evaluation in Serum

Serum total cholesterol level (TC), triglyceride (TG) level, high-density lipoproteins (HDL), total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) was determined by using standard kits from Transasia BioMedical Limited, Mumbai, India. The estimation procedure is obtained in detail from leaflets provided by the commercially available kits are as follows.

The biochemical indicator assessment was done from the each group with 10% w/v homogenate liver for determination of lipid peroxidation-malondialdehyde (MDA), reduce glutathione (GSH) level, superoxide dismutase (SOD) and catalase activity (CAT).

Statistical analysis

All statistical analysis is expressed as the mean ± standard error of the mean (SEM). Data were analyzed by one way ANOVA, where applicable $p<0.05$ was considered statistically significant, compared with vehicle followed by Dunnett's test.

Results

Effect of cannabigerolic acid on blood glucose level in STZ -induced diabetic rats

Blood glucose level of animals in all groups was recorded at 1, 8th and 21th day. Progressive decrease in blood glucose level was found in all treatment groups during study. At the end of experiment, glibenclamide 5 mg/kg

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p.o. (115.00 ± 5.00), cannabigerolic acid 50 and 100 mg/kg/p.o., (129.00 ± 6.50; 122.00 ± 7.00) treated group blood glucose level was decrease significantly ($p<0.05$) at 21st days (Table 1).

Effect of cannabigerolic acid on TC level in STZ -induced diabetic rats

In cannabigerolic acid (CBGA) 50 and 100 mg/kg/p.o., (135.0 ± 5.00; 125.5 ± 4.50) were decreased significantly ($p < 0.05$) TC. In 5 mg/kg glibenclamide (119.0 ± 5.00) treated group TC decreased significantly ($p < 0.05$), respectively as compared with control group (250.0 ± 5.00) (Table 2).

Effect of cannabigerolic acid on TG level in STZ -induced diabetic rats

In cannabigerolic acid 50 and 100 mg/kg/p.o., (122.00 ± 8.00; 100.50 ± 8.00) were decreased significantly ($p < 0.05$) TG. In 5 mg/kg glibenclamide (99.00 ± 9.00) treated group TG decreased significantly ($p < 0.05$), respectively as compared with control group (199.5 ± 6.50) (Table 2).

Effect of cannabigerolic acid on HDL in STZ-induced diabetic rats

Cannabigerolic acid 50 and 100 mg/kg (45.10±1.90; 48.00±1.37) treated group HDL also decreased significantly ($p<0.05$). In 5 mg/kg p.o. glibenclamide (49.78±2.03) treated group HDL increased significantly ($p<0.001$), respectively as compared with control group (30.48±2.87) (Table 2).

Effect of cannabigerolic acid on LDL in STZ -induced diabetic rats

Cannabigerolic acid 50 and 100 mg/kg (65.5± 2.50; 57.4± 2.00) treated group LDL also decreased significantly ($p<0.05$). In 5 mg/kg p.o. glibenclamide (49.4± 2.00) treated group LDL was significantly decreased ($p<0.001$), respectively as compared with control group (179.62± 2.50) (Table 2).

Effect of cannabigerolic acid on TP level in STZ-induced diabetic rats

Cannabigerolic acid 50 and 100 mg/kg (87.00 ± 5.00; 83.00 ± 7.00) treated group TP also decreased significantly ($p<0.01$). In 5 mg/kg p.o. glibenclamide (80.01 ± 9.00) treated group TP was significantly decreased ($p<0.001$), respectively as compared with control group (140.50± 6.50) (Table 2).

Effect of cannabigerolic acid on AST in STZ -induced diabetic rats

After end days of experiment, serum transaminase such as AST level was significantly ($p < 0.001$) elevated in diabetic control group. Cannabigerolic acid 50 and 100 mg/kg (68.40 ± 5.5060.20 ± 5.50) treated group AST also decreased significantly ($p<0.01$). In 5 mg/kg p.o. glibenclamide (57.50 ± 5.50) treated group AST was significantly decreased ($p<0.001$), respectively as compared with control group (110.5 ± 7.50) (Table 3).

Effect of cannabigerolic acid on ALT in STZ-induced diabetic rats

ALT level was significantly ($p < 0.001$) elevated in diabetic control group. Cannabigerolic acid 50 and 100 mg/kg (50.50 ± 4.50; 47.50 ± 4.50) treated group ALT also decreased significantly ($p<0.01$). In 5 mg/kg p.o. glibenclamide (40.00 ± 4.00) treated group ALT was significantly decreased ($p<0.001$), respectively as compared with control group (110.0 ± 10.00) (Table 3).

Effect of cannabigerolic acid on insulin in STZ-induced diabetic rats

In comparison to the diabetic control, cannabigerolic acid 50 and 100 mg/kg (1.58 ± 0.05; 1.60 ± 0.05) and glibenclamide 5 mg/kg p.o. (1.66 ± 0.09) administration significantly ($p < 0.01$) increased serum insulin levels as compared to control group (1.00 ± 0.05) (Table 3).

Effect of Cannabigerolic acid on SOD level in rats

From antioxidant study, it was found that in STZ-induced diabetic control group (8.50±0.5), SOD level was decreased significantly ($p < 0.001$), while in treated group, with Cannabigerolic acid 50 and 100 mg/kg (11.9±0.5; 12.5±0.5) and glibenclamide 5 mg/kg p.o. (13.5±0.5) were significantly ($p < 0.001$) increased SOD level (Table 4).

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Effect of cannabigerolic acid on lipid peroxidation level in rats

In STZ-induced diabetic control group (41.50±0.81) lipid peroxidation was found to be increased significantly ($p < 0.001$), while in Cannabigerolic acid 50 and 100 mg/kg (25.80±0.51; 23.44±0.40) and glibenclamide 5 mg/kg p.o. (21.28±0.81) were significant decrease found in lipid peroxidation ($p>0.05$) (Table 4).

Effect of Cannabigerolic acid on CAT level in rats

In STZ induced diabetic control group (8.42±2.5) CAT was found to be decreased significantly ($p < 0.001$), while in Cannabigerolic acid 50 and 100 mg/kg (13.56±2.4; 14.30±2.5) and glibenclamide 5 mg/kg p.o. (15.68±2.5) were significant increase in CAT ($p>0.05$) (Table 4).

Effect of Cannabigerolic acid on GSH level in rats

In STZ-induced diabetic control group (20.50±2.5) GSH was found to be decreased significantly ($p < 0.001$), while in CBGA 50 and 100 mg/kg (33.50±2.6; 39.10±2.3) and glibenclamide 5 mg/kg p.o. (40.20±2.5) were significant increased found in GSH ($p>0.05$) (Table 4).

Discussion

In the present study, the effects of cannabigerolic acid on diabetes were assessed using STZ -induced diabetic rat model. The administration of cannabigerolic acid for 21st days resulted in a significant reduction in blood glucose levels and lipid profile. Diabetes mellitus is a type of metabolic disorders marked characterized by increase in blood glucose levels as result of abnormality occurs in either insulin secretion or insulin utilization. This metabolic impairment leads to abnormal functioning of carbohydrate; lipids, and proteins. Significant consistent rise in blood glucose level clinical known as hyperglycemia, consider contributing factor for developing the micro and macrovascular complications such as nephropathy, neuropathy, retinopathy, and cardiovascular complications. The recent figures indicated that by 2025 more than 300 million of populations were suffer from diabetes worldwide. The most common underlying contributing factor includes; obesity, carbohydrate rich diet, poor nutrition and sedentary life style. Indian traditional medicinal system known to mentioned various indigenous remedies for the treatment for diabetes mellitus [13]. Some previous report data demonstrated that around 5 percent of population worldwide affected with diabetes were faced adverse effects of drugs used for the management of diabetes mellitus and would be biggest challenges in front healthcare systems[13]. The effective prevention and treatment protocol has got centre of importance for clinically dealing with non-curable metabolic disorder such as diabetes mellitus to prevent any future complications associated with its management [14-16]. Earlier line of investigations elucidated the significance of STZ for the induction of induced Type 2 diabetes in experimental animal models. The molecular mode of action of STZ implicated its involvement as glucose analogue to beta cells of pancreas. Extension to this finding reported investigations also postulated that min. single dose of STZ (40mg/kg) successfully induced the diabetic responses in experimental animal model[17,18]. Based on this finding present study design implicated the use of STZ for induction of diabetes in experimental rats. In present investigation comparison analysis between normal saline control group with STZ treated group demonstrated that; STZ control group showed significant diabetogenic responses such as hyperglycemia, decrease in body weight, and certain biochemical profiles such lipid and proteins as clinical indications of diabetes mellitus similar to previously reported studies [19,20]. Similar to previous line of investigations, present study data also postulated that there is significant increase in body weight of all treatment group as compare to diabetic control group with significance of ($p<0.05$) at end of protocol. The underlying pathogenesis for weight reduction correlated with insulin deficiency which linked to cause catabolism of fats and proteins [19,20]. Furthermore, previous investigations also enlightened STZ treated group exert significantly increase in blood glucose level on day 8th and 21st as compare to normal control group indicated STZ treated group showed development of diabetes in experimental animal model which is clinically correlated with previous reported data[21]. In same experimental study standard treatment with glibenclamide showed significant reduction in blood glucose level on 8th day ($p<0.01$) and 21st day ($p<0.001$). In another experimental group treated with cannabigerolic acid with two different doses lower dose 50mg mg/kg/p.o. ($p<0.05$) and higher dose 100mg mg/kg/p.o. ($p<0.01$) significantly decreases the blood glucose level on day 21st of protocol. Earlier data explored the significant abnormal changes in various biochemical profiles (lipid profiles) associated with microvascular complications of diabetes mellitus. Earlier investigations have identified the significance of abnormal serum lipid levels in microvascular complications associated with diabetes[22]. Similarly, few investigators also postulated that experimental model for STZ significantly responsible for abnormal lipid counts and elevated hepatic triglycerides[22-25]. Similarly, present study also highlighted the same findings in based on that data obtained from previous investigations. In present study, STZ treated group exert significant increases serum level of TC; TG; LDL;TP; and serum ALT as well as AST levels as compare to

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normal control group ($p<0.001$) and significantly decreases serum levels of HDL($p<0.001$) [26,27]. In same line of investigation in another group treated with standard drug glibenclamide remarkably decreases the serum levels of TC; TG; LDL;TP; and serum ALT as well as AST levels ($p<0.001$) and increases the serum levels of HDL ($p<0.001$) at the end of the experimental study. In another experimental group treated with cannabigerolic acid with lower dose 50mg mg/kg/p.o. less significantly decreases ($p<0.05$) decreases TG, serum AST; moderately decreases ($p<0.01$) TG, LDL, ALT, and more significantly ($p<0.001$) decreases TP, and MDA[28] whereas, more significantly increases SOD, CAT and GSH[29] level in serum and moderately significant increases serum HDL level ($p<0.01$). Similarly, higher dose 100mg mg/kg/p.o. cannabigerolic acid less significantly decreases triglyceride; moderate significantly decreases AST and ALT levels ($p<0.01$); more significantly decreases total cholesterol; LDL; triglyceride; total protein; and MDA ($p<0.001$), whereas, significantly increases serum levels of HDL; insulin; SOD; CAT and GSH levels ($p<0.001$) [30-31].

Conclusion

The present study findings indicated that the usefulness of the cannabigerolic acid streptozotocin- induced diabetic rats. Our study suggested that cannabigerolic acid dose-dependently produced antidiabetic activity. In this study might be helpful to understand the role of cannabigerolic acid in the clinical treatment of diabetes mellitus.

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Table No. –1: Antidiabetic activity of Cannabigerolic acid (CBGA) and Cannabis sativa on blood glucose level in STZ-induced diabetic rats

Groups	Treatment	Dose	Blood glucose (mg/dl)		
			Days 1	Days 8	Days 21
I	Normal	1 % saline	81.00 ± 5.00	86.00 ± 5.00	100.00 ± 5.00
II	Control	40 mg/kg i.p.	291.00 ± 7.00	387.00 ± 8.00$^{\#}$	390.00± 8.00$^{\#}$
III	Glibenclamide	5 mg/kg p.o.	250.00± 6.40	150.00 ± 6.50**	115.00 ± 5.00***
IV	Cannabigerolic acid (CBGA)	50 mg/kg p.o.	251.00 ± 7.00	150.20 ± 7.00*	129.00 ± 6.50*
V	Cannabigerolic acid (CBGA)	100 mg/kg p.o.	250.00± 7.00	148.10 ± 7.00*	122.00 ± 7.00**

Values are expressed as mean ± S.E.M. (n = 6).Values are statistically significant at $p<0.05$ (One-way ANOVA followed by Dunnett's test).

Table No. –2: Effect of Cannabigerolic acid on lipid profile in STZ -induced diabetic rats

Group	Drug	Dose	Total Cholesterol (mg/dl)	Triglyceride (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	TP (g/dl)
I	Normal	1 % saline	80.50 ± 5.50	85.00 ± 8.00	20.63± 2.00	50.87±1.13	60.00± 8.00
II	Control	40 mg/kg i.p.	250.0 ± 5.00	199.5 ± 6.50	179.62± 2.50	30.48±2.87	140.50± 6.50
III	Glibenclamide	5 mg/kg p.o.	119.0 ± 5.00***	99.00 ± 9.00**	49.4± 2.00***	49.80±2.03***	80.01 ± 9.00***

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IV	Cannabigerolic acid (CBGA)	50 mg/kg p.o.	135.0 ± 5.00**	122.00 ± 8.00*	65.5± 2.50***	45.10±1.90**	87.00 ± 5.00***
V	Cannabigerolic acid (CBGA)	100 mg/kg p.o.	125.5 ± 4.50***	100.50 ± 8.00*	57.4± 2.00***	48.00±1.37***	83.00 ± 7.00***

Values are expressed as mean ± S.E.M. (*n* = 6).Values are statistically significant at p<0.05 (One-way ANOVA followed by Dunnett's test).

Table No. –3: Effect of Cannabigerolic acid on biochemical parameters in STZ -induced diabetic rats

Group	**Drug**	**Dose**	**AST (IU/L)**	**ALT (IU/L)**	**Insulin (ng ml^{-1})**
I	Normal	1 % saline	50.00 ± 5.00	33.00 ± 5.00	1.74 ± 0.13
II	Control	40 mg/kg i.p.	110.5 ± 7.50	110.0 ± 10.00	1.00 ± 0.05
III	Glibenclamide	5 mg/kg p.o.	57.50 ± 5.50***	40.00 ± 4.00**	1.66 ± 0.09***
IV	Cannabigerolic acid (CBGA)	50 mg/kg p.o.	68.40 ± 5.50*	50.50 ± 4.50**	1.58 ± 0.05**
V	Cannabigerolic acid (CBGA)	100 mg/kg p.o.	60.20 ± 5.50**	47.50 ± 4.50**	1.60 ± 0.05***

Values are expressed as mean ± S.E.M. (*n* = 6).Values are statistically significant at p<0.05 (One-way ANOVA followed by Dunnett's test).

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Table No. –4: Effect of Cannabigerolic acid on SOD, MDA, CAT and GSH in STZ -induced diabetic rats

Group	Drug	Dose	SOD (U/mg protein)	lipid peroxidation (nM of MDA / min×mg protein)	CAT	GSH
I	Normal	1 % saline	15.50±0.7	15.67±0.79	13.80±2.5	45.50±2.5
II	Control	40 mg/kg i.p.	8.50±0.5	41.50±0.81	8.42±2.5	20.50±2.5
III	Glibenclamide	5 mg/kg p.o.	13.5±0.5 ***	21.28±0.81***	15.68±2.5***	40.20±2.5***
IV	Cannabigerolic acid (CBGA)	50 mg/kg p.o.	11.9±0.5 ***	25.80±0.51***	13.56±2.4***	33.50±2.6***
V	Cannabigerolic acid (CBGA)	100 mg/kg p.o.	12.5±0.5 ***	23.44±0.40***	14.30±2.5***	39.10±2.3***

Values are expressed as mean ± S.E.M. (n = 6).Values are statistically significant at $p<0.05$ (One-way ANOVA followed by Dunnett's test).